Docket No.: PC-0059 US
Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

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By: _____ Printed: **Jeannie G. Labra**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Chen et al.

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Title: MUCIN-RELATED TUMOR MARKER

Serial No.: 09/840,746 Filing Date: April 23, 2001

Examiner: Davis, M. Group Art Unit: 1642

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TRANSMITTAL FEE SHEET

Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard; and
2. Brief on Appeal, including Appendix (25 pp., in triplicate).

X	Fee for filing a Brief in support of an Appeal under 37 CFR 1.17(c):	$ 330.00
X	Please charge Deposit Account No. **09-0108** in the amount of :	$ 330.00

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 09-0108. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,

INCYTE CORPORATION

Date: October 20, 2003

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Docket No.: PC-0739 US

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Chen et al.

Title: MUCIN-RELATED TUMOR MARKER

Serial No.:	09/840,746	Filing Date:	April 23, 2001
Examiner:	Davis, M.	Group Art Unit:	1642

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Alexandria, VA 22313-1450

#16 KD 10/29/03

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed August 20, 2003, and received by the USPTO on August 25, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the

$ **330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1-6 of the above-identified application.

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(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc., (now Incyte Corporation, formerly known as Incyte Genomics, Inc.) (Reel 012006, Frame 0645) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1-6
Claims allowed:	(none)
Claims canceled:	Claims 13-20
Claims withdrawn:	Claims 7-12
Claims on Appeal:	Claims 1-6 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection beyond the cancellation of non-elected claims 13-20 in the Response to Final Office Action filed August 4, 2003.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to polynucleotides encoding a mucin-related tumor marker (MRTM:SEQ ID NO:1) based on sequence homology with two mucin proteins, MUC3 and PGM-9B, and the conservation of various amino acid sequence domains characteristic of membrane-bound, extracellular proteins of the mucin family. See specification, at page 10, and Figures 2A-2F. Mucins are described in the specification and the art of record as membrane-bound epithelial glycoproteins involved in epithelial cell protection, adhesion modulation and regulation, and signaling, many of which are valuable cell-surface tumor markers of clinical significance. See specification, at pages 2-3. MRTM was further shown to be differentially expressed in a human breast tumor cell line relative to non-tumorigenic breast cell lines by microarray analysis. See specification, at pages 9-10 and Table 1. The claimed polynucleotides

are therefore asserted to be useful in the diagnosis and treatment of cancer, in particular, breast cancer, and in toxicology testing and drug discovery, particularly related to breast cancer. See specification, at page 9, lines 21-24, at page 14, lines 7-11, and at page 21, lines 18-25.

(6) ISSUES

1. Whether claims 1-6 directed to MRTM encoding polynucleotide sequences meet the utility requirement of 35 U.S.C. §101, e.g., whether there is evidence that the sequence homology between the protein coded for by the claimed nucleic and another mucin protein, MUC3, known to have utility as a tumor marker, demonstrates a "substantial likelihood" of utility under 35 U.S.C. § 101. Whether the differential expression of transcripts of the polynucleotide encoding MRTM in a human breast cancer cell line relative to normal breast cells demonstrates a "substantial likelihood" of use of the claimed polynucleotide in the detection and diagnosis of breast cancer.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

3. Whether polynucleotides encoding naturally occurring variants of the amino acid sequence of SEQ ID NO:1 having at least 90% sequence identity to SEQ ID NO:1 are sufficiently disclosed in the specification to meet the written description requirements of 35 U.S.C. §112, first paragraph. In particular, whether or not the written description standard is fulfilled by both what is specifically disclosed in the specification and what is conventional or well known to one skilled in the art such that the skilled artisan would recognize applicants possession of said variants at the time the application was filed.

4. Whether claims 1 and 3-6 are sufficiently enabled under 35 U.S.C. §112, first paragraph for a polynucleotide "encoding " a polypeptide of SEQ ID NO:1. In particular, whether there is evidence that the polypeptide of SEQ ID NO:1 is enabled based on sequence homology with mucin proteins of established utility, and secondly, whether or not the expression

of the mRNA encoding SEQ ID NO:1 presents a "substantial likelihood" that the encoded protein is similarly expressed.

5. Whether the recited variants of SEQ ID NO:1 and SEQ ID NO:2, as recited in claims 1(b) and 2(b), are sufficiently enabled by a specific and substantial utility that the skilled artisan would know how to use the claimed invention in accordance with 35 U.S.C. §112, first paragraph

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

All of the claims on appeal are grouped together.

As to Issue 4

Claims 1 and 3-6 are grouped together.

As to Issue 5

Claims 1, 2, and 3-6 are grouped together

(8) APPELLANTS' ARGUMENTS

The rejection of claims 1-6 under 35 U.S.C. §§ 101 and 112, first paragraph is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The Examiner has maintained her rejection of claims 1-6 under 35 U.S.C. § 101 and § 112, first paragraph for lack of a specific and substantial utility or a well established utility based primarily on an allegation that human tumor cell lines, derived from humor tumors, are generally unsuitable models for studying human cancers. In particular, the Examiner stated that there is widespread belief in the scientific community that they (tumor cell lines) are not representative of the tumors from which they are derived, due to extensive chromosomal rearrangements,

oncogene mutations, and multiple sites of allelic loss and gene amplification, including breast carcinoma. The Examiner cited applicants reference to Wistuba, et al. (1998), in particular, at page 2931, second column, in support of this statement, in addition to various other references cited in the Office Action mailed 1/13/2003, Paper No. 10. The Examiner further noted that the BT20 human tumor cell line, used in the present study, does not appear to be among those studied by Wistuba et al., and therefore that it is unpredictable that the cell line BT20 has any of the properties of the cell lines studied by Wistuba et al., and retain many of the properties of their parental tumors, and one cannot determine whether the putative overexpression of the claimed sequence in the breast cell line BT20 is not due to cell culture artifacts. See Final Office Action, at page 4.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in humans. The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of mucin proteins, whose cell surface expression and differential expression in various tumors has provided valuable tumor markers for clinical diagnosis of cancer. See specification, at page 3. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions.

Appellants have previously submited the Declaration of Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. See Response to Final Office Action, filed August 4, 2003. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on April 23, 2001] that cDNA microarrays that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection

> with conducting gene expression monitoring studies on proposed (or actual) drugs for treating breast cancer for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. The use of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration previously submitted on August 3, 2003. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Chen 746 application on April 23, 2001 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[1]

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Chen 746 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

In connection with his explanations, Dr. Bedilion states that the "Chen '746 specification would have led a person skilled in the art on April 23, 2001 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of breast cancer [a] to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on April 23, 2001] that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating breast cancer for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-April 23, 2001 publications showing the state of the art on April 23, 2001 (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts [(a)-(f)], he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development in October 2000 (and for several years prior to October 2000) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Chen '746 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Chen '746 application at the time it was filed "would have wanted their cDNA microarray to have a SEQ ID NO:1-encoding polynucleotide probe because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to April 23, 2001" (Bedilion Declaration, ¶ 15, item (f)). This, by itself,

provides more than sufficient reason to compel the conclusion that the Chen '746 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on p. 14 of the Chen '746 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-April 2001 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Chen '746 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized

> nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Chen '746 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999)[2].

In another pre-April 2001 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

Efforts have been directed toward the amplification of each predicted ORF or any

> other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

[2]Nucleic acids useful for measuring the expression of whole classes of genes are routinely

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[2]Note that this and other references cited in this brief were previously submitted in the response filed August 4, 2003.

incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and

validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

C. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that

polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities.(Final Officce Action, at p.2). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Because the uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include: e.g., for chromosomal markers, probes,and in forensics analysis.

C. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to ignoring the specific and substantial utilities for the claimed invention in toxicology testing and drug discovery discussed above, the Examiner disputes applicants' asserted utility based on differential expression of the claimed polynucleotide in breast cancer as determined by microarray analysis as described at pages 36-37 of the specification. The Examiners' position is based primarily on two allegations: (1) that the BT20 human breast cancer cell line, derived from human breast cancer tissue, is not generally accepted as a suitable *in vitro* model for human breast cancer, and (2) that, in any case, since Table 1 is the result of electronic Northern analysis, as disclosed at page 35 of the specification, the findings are "not credible" based on the Examiners' allegation that cDNA libraries used in such analyses are "underrepresentative" of the actual number of genes expressed in the tissues from which they are derived. See Final Office Action, at page 5.

With respect to (1), above, appellants reiterate arguments previously presented in both the Response to Office Action, flied 4/02/2003, and the Response to Final Office Action, filed 8/4/2003, that the Examiner has not met her burden of proof in refuting application asserted utility based on the data from Table 1. In particular, applicants reviewed, in detail, the references cited by the Examiner in the Office Action mailed 1/13/2003 alleging to support her position that it is well known in the art that cell lines are generally recognized as unsuitable models for the study of human cancers. None of these articles provide the basis for such a sweeping conclusion. Further, applicants submitted several additional references that support the use of tumor cell lines, in particular the BT20 cell line of the instant invention, in modeling human cancers. See Response to Office Action, filed 4/02/2003, at pages 8-9. In the Final Office Action, the Examiner has ignored applicants rebuttal, dismissing it as "unpersuasive" and reiterating previous argumments, relying heavily on the Witsuba article cited by applicants in the IDS. In particular, the Examiner cites Wistuba et al. in the second paragraph of the "Introduction" where the author specifically states that "there is widespread belief in the scientific community that they (tumor cell lines) are not representative of the tumors from which they are derived". It is clear, however, that the Examiner takes this statement out of context because the author himself disagrees with this assessment stating at the end of the same paragraph, "However, as far as we could determine, no detailed comparison of

the properties of human cell lines with those of the tumors from which they were derived has been published for any cancer type". The paper then goes on to report the findings of 18 human breast cancer cell lines compared with their archival tumor tissues, and concludes (at the bottom of page 2937) that "Thus, breast carcinoma cell lines are useful models for studying at least one major form of breast cancer".

With respect to point (2) above, applicants reiterate as stated in the Response to Final Office Action, at page 4, that the data of Table 1 is not derived from electronic Northern analysis as the Examiner alleges, but from wet lab experiments conducted in a microarray format. See specification, at bottom of page 5 to top of page 6, and at pages 36-37, Examples X and IX. Nevertheless, applicants also challenged the veracity of the Examiners' contention that cDNA databases, such as the LIFESEQ database recited in the instant specification, are "underepresentative" of actual expressed genes because it is generally accepted that ""cells in the human body encode approximately 100,000 genes of which between 10,000 and 20,000 are thought to be expressed as mRNA" (See Final Office Action, at page 5; and applicants response, at page 5). Applicants also provided evidence from a published article showing that the most recent estimates of the human genome projected approximately 30,000 genes, considerably less than the Examiners' "generally accepted" figure of approximately 100,000.

Thus, applicants reiterate that the Examiner has not established by a preponderance of evidence that the skilled artisan would reasonably doubt applicants asserted use the claimed invention in the detection and diagnosis of breast cancer based on differential expression analysis.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to

how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax," to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specification as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

The rejection of claims 1(b), 2(b) and 3-6 under 35 U.S.C. § 112, First Paragraph for lack of written description is improper as the inventions of those claims are sufficiently described in chemical and structural terms that one of skill in the art would recognize applicants possession of them

In the Final Office Action, at pages 6-9, the Examiner reiterated allegations previously presented (in the Office Action filed 1/13/2003) that applicants have not sufficiently described claimed variants of the polypeptide of SEQ ID NO:1 (as described in claim 1(b)), or of the polynucleotide of SEQ ID NO:2 (as described in claim 2(b)), such that the skilled artisan would recognize applicants possession of them at the time the application was filed.

In the Response to Office Action filed 4/02/2003, specifically at pages 10-14, applicants

provided ample evidence in compliance with Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, that the claimed variants of the polynucleotides encoding SEQ ID NO:1, and of SEQ ID NO:2, were described in sufficient terms of structural, chemical, and physical properties that, coupled with what is conventional or well known to one skilled in the art, the skilled artisan would readily recognize applicants possession of the claimed variants at the time the application was filed. Since the Final Office Action presents no new arguments or evidence rebutting applicants previous arguments and evidence, appellants reassert that the specification provides an adequate written description of the claimed variant sequences, and withdrawal of the rejection of claims 1(b), 2(b) and 3-6 under 35 U.S.C. § 112, first paragraph is therefore requested.

The Examiner's rejection of claims 1 and 3-6 under 35 U.S.C. § 112, First Paragraph, for lack of enablement for a polynucleotide "encoding" the polypeptide of SEQ ID NO:1 is improper because of the substantial likelihood that the polypeptide of SEQ ID NO:1 and the polynucleotide of SEQ ID NO:2 are similarly expressed

The Examiners' allegation that polynucleotide expression does not "insure" that the encoded polypeptide is similarly expressed, thus enabling a polypeptide based on expression of the encoding polynucleotide, was addressed in the Response to Office Action, filed 4/02/2003, specifically at pages 15-16. In response to this rebuttal in the Final Office Action, the Examiner merely replied that the Lewin article, cited by applicants as evidence of the generally accepted knowledge that polynucleotide expression leads to and generally reflects protein expression, does not support applicants position because the Lewin does not specifically disclose "a correlation between mRNA and protein levels of expression". See Final Office Action, at page 10. Appellants reiterate that, as stated in the Response to Office Action, filed 4/02/2003, the Lewin article clearly teaches that polynucleotide expression (i.e., gene transcription) is the "most common level of regulation" for gene and protein expression, and that the " overwhelming majority of regulatory events occur at the initiation of transcription ". Thus, the mere fact that the article does not disclose experimental data correlating mRNA and protein levels does not detract from the factual basis for the statements made that support applicants contention that the Examiners' evidence for the "potential" for post-transcriptional regulation of SEQ ID NO:1 expression does not provide specific evidence that one skilled in the art would doubt the substantial likelihood that the expression of SEQ ID NO:1 is, like most genes, controlled at the

transcriptional level and therefore likely correlated with levels of SEQ ID NO:2 mRNA expression. Withdrawal of the rejection of claims 1 and 3-6 under 35 U.S.C. § 112, first paragraph is therefore requested.

The rejection of claims 1(b), 2(b) and 3-6 under 35 U.S.C. § 112, First Paragraph, for a lack of enablement of the claimed variants is improper as these inventions are enabled by the utilities established for the parent molecules, SEQ ID NO:1 and SEQ ID NO:2

In the Final Office Action, the Examiner reiterated her allegation that, because the specification has not taught a specific and substantial utility for the polynucleotide encoding SEQ ID NO:1or the polynucleotide of SEQ ID NO:2, the claimed variants of these sequence are not enabled, i.e., the skilled artisan would not know how to use them.

Appellants have previously established a utility for the polynucleotide of SEQ ID NO:2 and the polypeptide of SEQ ID NO:1 for the reasons discussed previously in this brief. Therefore the use of the claimed variants, for example, "in hybridization, amplification, and screening technologies to identify and distinguish among SEQ ID NO:2 and related molecules in a sample" as recited at page 11, lines 24-25, is fully enabled by the specification. Withdrawal of the rejection of claims 1(b), 2(b) and 3-6 under 35 U.S.C. § 112, first paragraph is therefore requested.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,

INCYTE CORPORATION

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APPENDIX - CLAIMS ON APPEAL

1. An isolated cDNA or the complement thereof comprising a nucleic acid sequence encoding a protein selected from:

    a) an amino acid sequence of SEQ ID NO:1; and

    b) a naturally occurring variant of SEQ ID NO:1 having at least 95% identity to the amino acid sequence of SEQ ID NO:1.

2. An isolated cDNA comprising a nucleic acid sequence selected from:

    a) SEQ ID NO:2 or the complement thereof; and

    b) a naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity to SEQ ID NO:2, or the complement thereof.

3. A composition comprising the cDNA or the complement of the cDNA of claim 1 and a labeling moiety.

4. A vector comprising the cDNA of claim 1.

5. A host cell comprising the vector of claim 4.

6. A method for using a cDNA to produce a protein, the method comprising:

    a) culturing the host cell of claim 5 under conditions for protein expression; and

    b) recovering the protein from the host cell culture.